

CLAIMS

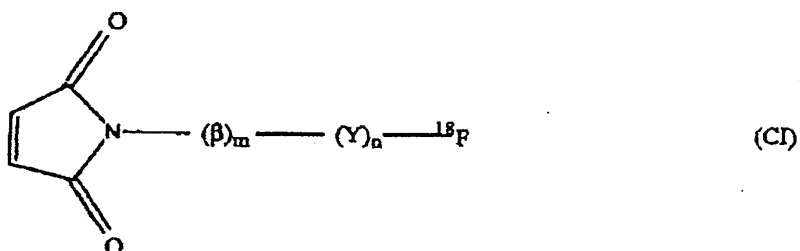
1. Peptide labelled with fluorine-18, characterized in that it comprises the following peptide sequence  
5 (PI):

J<sup>1</sup>-J<sup>2</sup>-J<sup>3</sup>-J<sup>4</sup>-J<sup>5</sup>-J<sup>6</sup>-Z<sup>7</sup>-U<sup>8</sup>-J<sup>9</sup>-J<sup>10</sup>-U<sup>11</sup>-Arg-J<sup>13</sup>-J<sup>14</sup>-U<sup>15</sup>-Lys-  
Gly-X<sup>18</sup>-Gly-Thr-J<sup>21</sup>-Glu-J<sup>23</sup>-J<sup>24</sup>-U<sup>25</sup>-J<sup>26</sup>-J<sup>27</sup>-J<sup>28</sup>-U<sup>29</sup>-J<sup>30</sup>-J<sup>31</sup>-  
Arg-J<sup>33</sup>-J<sup>34</sup>-J<sup>35</sup>-J<sup>36</sup>-B<sup>37</sup>-J<sup>38</sup>-J<sup>39</sup>-U<sup>40</sup>-J<sup>41</sup>-J<sup>42</sup>-J<sup>43</sup>-U<sup>44</sup>-J<sup>45</sup>-J<sup>46</sup>-J<sup>47</sup>-  
J<sup>48</sup>-J<sup>49</sup>-Arg-J<sup>51</sup>-U<sup>52</sup>-J<sup>53</sup>-J<sup>54</sup>-Asp-U<sup>56</sup>-Lys-Ser-Z<sup>59</sup>-Leu-J<sup>61</sup>-J<sup>62</sup>-  
J<sup>63</sup>-J<sup>64</sup>-Z<sup>65</sup>-J<sup>66</sup>-J<sup>67</sup>-U<sup>68</sup>-J<sup>69</sup>-J<sup>70</sup>-J<sup>71</sup>-U<sup>72</sup>-J<sup>73</sup>-J<sup>74</sup>-J<sup>75</sup> (I)

10 in which J, Z, U, X and B represent amino acids such that:

- the amino acids J are chosen independently of each other from natural amino acids, or derivatives thereof, in such a manner that at least 50% of them are polar residues chosen from Arg, Asn, Asp, 15 Cys, Gln, Glu, Gly, His, Lys, Orn, Pro, Ser, Thr and Tyr,
  - the amino acids U are chosen from Ala, Cys, Gly, Ile, Leu, Met, Phe, Trp, Tyr and Val,
  - the amino acid X<sup>18</sup> is chosen independently of the 20 other amino acids of the sequence from Ala, Asn, Cys, Gln, Gly, His, Ile, Leu, Met, Phe, Ser, Thr, Trp, Tyr and Val,
  - the amino acid B<sup>37</sup> is chosen independently of the other amino acids of the sequence from Arg, Ala, 25 Cys, Gly, Ile, Leu, Met, Phe, Trp, Tyr and Val,
  - the amino acid Z<sup>7</sup> is chosen independently of the other amino acids of the sequence from Asp and Glu,
  - the amino acids Z<sup>59</sup> and Z<sup>65</sup> are chosen 30 independently from Glu, Asp, Lys and Arg,
- the superscripts of J, Z, U, X and B representing the positions of these amino acids in the said sequence,

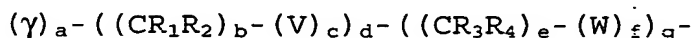
the said peptide being labelled directly or indirectly with a compound (CI) of general formula:



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in which:

- m represents an integer from 0 to 10, such as 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10;
- n represents an integer from 0 to 10, such as 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10;
- Y represents a group chosen from alkyl groups, monocyclic or bicyclic heterocyclic groups chosen from imidazolyl, pyrazolyl, benzimidazolyl, pyridinyl, piridazinyl, pyrimidinyl, pyrazinyl, triazinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl and purinyl groups, it being possible for Y to be optionally substituted with one or more substituents, each of these substituents being chosen independently from hydrogen, (nonradioactive) halogens, phenyl, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, aryloxy, amino, mono- or di(C<sub>1-6</sub> alkyl)amino, mono- or di(aryl)amino, thio, C<sub>1-6</sub> alkylthio, arylthio, formyl, C<sub>1-6</sub> alkylcarbonyl, arylcarbonyl, carbonyl, C<sub>1-6</sub> alkoxy carbonyl, aryloxy carbonyl, C<sub>1-6</sub> alkylaminocarbonyl, arylaminocarbonyl and trifluoromethyl groups;
- β represents a radical of formula:



30

in which:

- a, b, c, d, e, f, g each independently represent an integer from 0 to 10, such as 0, 1, 2, 3, 4, 5, 6, 7, 8, 9;

- γ, V and W each independently represent -NR<sub>1</sub>-, -O-,

5                     $\begin{array}{c} \text{O} \\ | \\ \text{---N---} \end{array}$ , ethynyl, -CR<sub>1</sub>=CR<sub>2</sub>-, -(C=O)-, -(C=S)-,  
-C(=NR<sub>1</sub>)-, -C(=O)O-, -(C=S)S-, -C(=NR<sub>1</sub>)NR<sub>2</sub>-,  
-CR<sub>1</sub>R<sub>2</sub>-, -CR<sub>1</sub>OR<sub>2</sub>-, -CR<sub>1</sub>NR<sub>2</sub>R<sub>3</sub>-, where R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub>  
are independently chosen from hydrogen, halogens,  
10                    phenyl, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, aryloxy, amino,  
mono- or di(C<sub>1-6</sub> alkyl)amino, mono- or  
di(aryl)amino, thio, C<sub>1-6</sub> alkylthio, arylthio,  
formyl, C<sub>1-6</sub> alkylcarbonyl, arylcarbonyl, carbonyl  
(C<sub>1-6</sub>)alkoxycarbonyl, aryloxycarbonyl, C<sub>1-6</sub>  
alkylaminocarbonyl, arylaminocarbonyl and  
15                    trifluoromethyl groups, directly or indirectly on  
an -SH functional group.

2. Peptide labelled with fluorine-18 according to  
Claim 1, in which the amino acids J are chosen  
20                    independently of each other from Ala, Arg, Asn, Asp,  
Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro,  
Ser, Thr, Trp, Tyr, and Val in such a manner that at  
least 50% of them are polar residues chosen from Arg,  
Asn, Asp, Cys, Gln, Glu, Gly, His, Lys, Pro, Ser and  
25                    Thr.

3. Peptide labelled with fluorine-18 according to  
Claim 1, in which the amino acids U and B of the  
sequence (PI) are chosen according to one of Examples  
30                    a) to j) presented in Table 1 below:

	U <sup>8</sup>	U <sup>11</sup>	U <sup>15</sup>	U <sup>25</sup>	U <sup>29</sup>	B <sup>37</sup>	U <sup>40</sup>	U <sup>44</sup>	U <sup>52</sup>	U <sup>56</sup>	U <sup>68</sup>	U <sup>72</sup>
Ex a)	Val	Leu	Met	Ile	Leu	Arg	Ile	Tyr	Leu	Leu	Val	Leu
Ex b)	Ala	Ile	Ile	Ile	Leu	Arg	Ile	Tyr	Leu	Leu	Ile	Leu
Ex c)	Ala	Ile	Ile	Ile	Leu	Arg	Ile	Tyr	Leu	Leu	Met	Val
Ex d)	Ala	Leu	Met	Leu	Leu	Arg	Ile	Tyr	Leu	Leu	Ile	Met
Ex e)	Ala	Leu	Met	Ile	Ile	Arg	Val	Tyr	Leu	Leu	Ile	Met
Ex f)	Ala	Leu	Met	Ile	Ile	Arg	Ile	Phe	Leu	Leu	Ile	Met
Ex g)	Ala	Leu	Met	Ile	Val	Arg	Ile	Phe	Leu	Leu	Ile	Phe
Ex h)	Val	Leu	Met	Ile	Leu	Arg	Ile	Phe	Leu	Leu	Ile	Met
Ex i)	Ala	Leu	Met	Ile	Leu	Arg	Ile	Phe	Leu	Leu	Ile	Met
Ex j)	Ala	Leu	Met	Ile	Leu	Arg	Ile	Tyr	Leu	Leu	Ala	Ala

(Ex = exemple)

(Ex = Example)

5 4. Peptide labelled with fluorine-18 according to Claim 1, in which the peptide sequence is chosen from the sequence ID No. 1, ID No. 2, ID No. 3, ID No. 4, ID No. 5, ID No. 6, ID No. 7, ID No. 8, ID No. 9, ID No. 10, ID No. 11, ID No. 12, ID No. 13 and ID No. 14 of the appended sequence listing.

5. Peptide labelled with fluorine-18 according to any one of Claims 1 to 4, additionally comprising, linked to its N-terminal end, the amino acid sequence chosen from Gly-Ser-Cys and Gly-Cys-Ser.

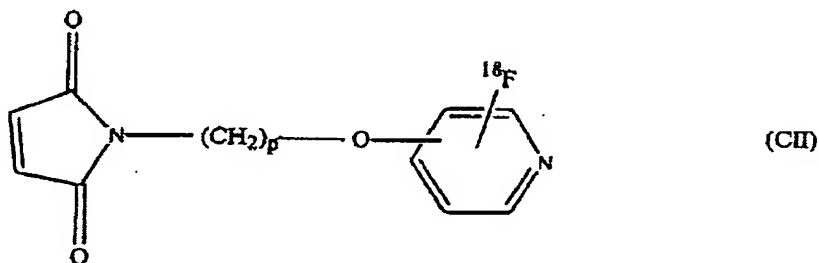
6. Peptide labelled with fluorine-18 according to any one of Claims 1 to 4, additionally comprising, linked to its N-terminal end, an amino acid sequence chosen from Gly-Ser-Gly-Cys, Gly-Cys-Gly-Ser and Gly-Cys-Gly-Cys.

7. Peptide labelled with fluorine-18 according to any one of Claims 1 to 6, in which the peptide is labelled directly with the compound (CI) by coupling the maleimide functional group of the compound (CI) with a free -SH functional group of the said peptide, for example the thiol functional group of a cystein of the peptide.

8. Peptide labelled with fluorine-18 according to any one of Claims 1 to 6, in which the peptide is labelled directly with the compound (CI) by coupling the maleimide functional group of the compound (CI) with a free -SH functional group of the peptide sequence (PI), for example the thiol functional group of a cystein of the peptide sequence.

9. Peptide labelled with fluorine-18 according to any one of Claims 1 to 6, in which, in the compound of formula (CI),  $n = 1$ , and Y is a 3-pyridinyl group.

10. Peptide labelled with fluorine-18 according to Claim 9, in which the compound (CI) corresponds to the following formula (CII):



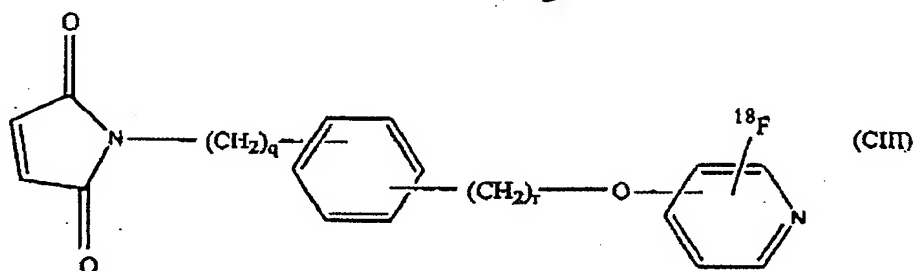
in which  $p$  is an integer from 1 to 10, such as 2, 3, 4, 5, 6, 7, 8 or 9.

11. Peptide labelled with fluorine-18 according to Claim 10, in which the compound of formula (CII) is chosen from:

B 14023.3 EE .

- 1-[2-(2-[<sup>18</sup>F] fluoropyridin-3-yloxy)ethyl]pyrrole-2,5-dione;
- 1-[4-(2-[<sup>18</sup>F] fluoropyridin-3-yloxy)butyl]pyrrole-2,5-dione;
- 5 - 1-[5-(2-[<sup>18</sup>F] fluoropyridin-3-yloxy)pentyl]pyrrole-2,5-dione;
- 1-[6-(2-[<sup>18</sup>F] fluoropyridin-3-yloxy)hexyl]pyrrole-2,5-dione;
- 1-[(2-[<sup>18</sup>F] fluoropyridin-3-yloxy)methyl]pyrrole-2,5-dione;
- 10 - 1-[3-(2-[<sup>18</sup>F] fluoropyridin-3-yloxy)propyl]pyrrole-2,5-dione.

12. Peptide labelled with fluorine-18 according to  
 15 Claim 9, in which the compound of formula (CI) corresponds to the following formula (CIII):

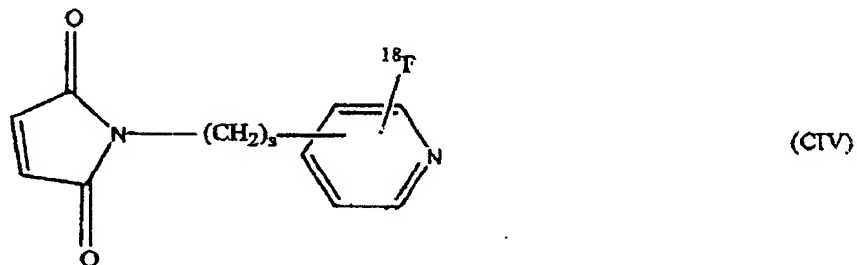


- 20 in which q and r represent independently an integer from 0 to 10, such as 0, 1, 2, 3, 4, 5, 6, 7, 8, 9.

13. Peptide labelled with fluorine-18 according to  
 Claim 12, in which the compound of the formula (CIII)  
 25 is chosen from:

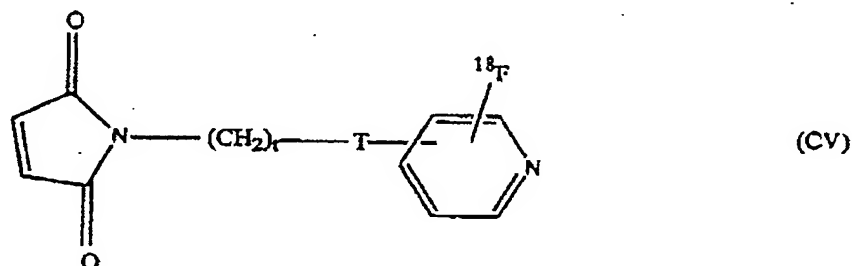
- 1-{4-[2-(2-[<sup>18</sup>F] fluoropyridin-3-yloxy)ethyl]phenyl}pyrrole-2,5-dione;
- 1-[4-(2-[<sup>18</sup>F] fluoropyridin-3-yloxymethyl)phenyl]pyrrole-2,5-dione;
- 30 - 1-[4-(2-[<sup>18</sup>F] fluoropyridin-3-yloxymethyl)benzyl]pyrrole-2,5-dione.

14. Peptide labelled with fluorine-18 according to Claim 9, in which the compound of formula (CI) corresponds to the following formula (CIV):



15. Peptide labelled with fluorine-18 according to Claim 14, in which the compound of formula (CIV) is 1-[3-(6-[ $^{18}F$ ]fluoropyridin-3-yl)propyl]pyrrole-2,5-dione.

16. Peptide labelled with fluorine-18 according to Claim 9, in which the compound of formula (CI) corresponds to the following formula (CV):



in which  $t$  is an integer from 0 to 10, such as 1, 2, 3, 4, 5, 6, 7, 8, 9 and  $T$  is a group  $-CH=CH-$  or  $-C\equiv C-$ .

17. Peptide labelled with fluorine-18 according to Claim 16, in which the compound (CV) is chosen from:

- 1-[3-(6-[ $^{18}F$ ]fluoropyridin-3-yl)allyl]pyrrole-2,5-dione;
- 1-[3-(6-[ $^{18}F$ ]fluoropyridin-3-yl)prop-2-ynyl]pyrrole-2,5-dione.

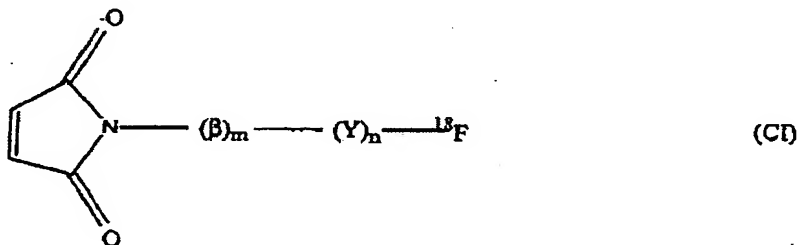
18. Peptide labelled with fluorine-18 according to any one of Claims 1 to 6,

in which the peptide sequence is chosen from the sequence ID No. 1, ID No. 2, ID No. 3, ID No. 4, ID No. 5, ID No. 6, ID No. 7, ID No. 8, ID No. 9, ID No. 10, ID No. 11, ID No. 12, ID No. 13 and ID No. 14 of the appended sequence listing,

in which the compound (CI) is chosen from:

- 1-[3-(6-[<sup>18</sup>F]fluoropyridin-3-yl)allyl]pyrrole-2,5-dione;
- 1-[3-(6-[<sup>18</sup>F]fluoropyridin-3-yl)prop-2-ynyl]pyrrole-2,5-dione.

19. Method for synthesizing a peptide labelled with a radioactive halogen according to any one of Claims 1 to 6, comprising a step for adding a compound (CI) of general formula:



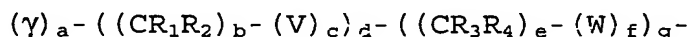
in which:

- m represents an integer from 0 to 10, such as 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10;
- n represents an integer from 0 to 10, such as 0, 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10;
- Y represents a group chosen from alkyl groups, monocyclic or bicyclic heterocyclic groups chosen from imidazolyl, pyrazolyl, benzimidazolyl, pyridinyl, piridazinyl, pyrimidinyl, pyrazinyl, triazinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, quinoxalinyl and purinyl groups, it being possible for Y to be optionally substituted with one or more substituents, each of these



substituents being chosen independently from hydrogen, halogens, phenyl, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, aryloxy, amino, mono- or di(C<sub>1-6</sub> alkyl)amino, mono- or di(aryl)amino, thio, C<sub>1-6</sub> alkylthio, arylthio, formyl, C<sub>1-6</sub> alkylcarbonyl, arylcarbonyl, carbonyl, C<sub>1-6</sub> alkoxycarbonyl, aryloxycarbonyl, C<sub>1-6</sub> alkylaminocarbonyl, arylaminocarbonyl and trifluoromethyl groups;

- β represents a radical of formula:



in which:

- a, b, c, d, e, f, g each independently represent an integer from 0 to 10, such as 0, 1, 2, 3, 4, 5, 6, 7, 8, 9;
- γ, V and W each independently represent -NR<sub>1</sub>, -O-

-S-,  $\begin{array}{c} \text{O} \\ | \\ \text{---N---} \end{array}$ , ethynyl, -CR<sub>1</sub>=CR<sub>2</sub>, -(C=O)-, -(C=S)-, -C(=NR<sub>1</sub>)-, -C(=O)O-, -(C=S)S-, -C(=NR<sub>1</sub>)NR<sub>2</sub>-, -CR<sub>1</sub>R<sub>2</sub>-, -CR<sub>1</sub>OR<sub>2</sub>-, -CR<sub>1</sub>NR<sub>2</sub>R<sub>3</sub>-, where R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are independently chosen from hydrogen, halogens, phenyl, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, aryloxy, amino, mono- or di(C<sub>1-6</sub> alkyl)amino, mono- or di(aryl)amino, thio, C<sub>1-6</sub> alkylthio, arylthio, formyl, C<sub>1-6</sub> alkylcarbonyl, arylcarbonyl, carbonyl (C<sub>1-6</sub>)alkoxycarbonyl, aryloxycarbonyl, C<sub>1-6</sub> alkylaminocarbonyl, arylaminocarbonyl and trifluoromethyl groups;

directly or indirectly onto an -SH functional group of a peptide.

20. Method according to Claim 19, in which the addition is carried out directly onto a free -SH functional group of the peptide sequence (PI), for example the thiol functional group of a cystein of the peptide sequence.

21. Kit for analysis and detection of negative charges at the surface of cells, characterized in that it comprises a peptide labelled with fluorine-18 according to any one of Claims 1 to 18.
22. Diagnostic kit comprising a peptide labelled with fluorine-18 according to any one of Claims 1 to 18.
23. Kit for analysis and detection of microvesicles in blood, characterized in that it comprises a peptide labelled with fluorine-18 according to any one of Claims 1 to 18.
24. Use of a peptide labelled with fluorine-18 according to any one of Claims 1 to 18 for the manufacture of a product intended for the detection of centres exposing negatively charged lipids at the surface of cells and/or the release of microvesicles into the blood.
25. Use according to Claim 24, in which the detection is a detection by means of scintigraphic images acquired by positron emission tomography (PET).
26. Composition for analysis and detection for example by positron emission tomography (PET) having a peptide labelled with fluorine-18 according to any one of Claims 1 to 18 and a pharmaceutically acceptable vehicle.
27. Composition for diagnosis, comprising a peptide labelled with fluorine-18 according to any one of Claims 1 to 18 and a pharmaceutically acceptable vehicle.